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Review Article

Dermatology Section

Treatment Modalities of Cutaneous and Genital Warts: A Narrative Review

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ABSTRACT

Human Papillomavirus (HPV) are non enveloped Deoxyribonucleic Acid (DNA) viruses, sized between 50-55 nm, that form two distinct groups to cause epithelial proliferation at cutaneous and mucosal surfaces, which are mostly benign. With more than 100 different HPV types, estimated 30-40 strains affect human genital tract. Of which, 16, 18, 31, 33, 35, 39, 45, 51, 52, and 5 are the oncogenic (high-risk) types associated with cervical, vulvar, vaginal, and anal cancers, and 6, 11, 40, 42, 43, 44, and 54 are non oncogenic (low-risk) types and are associated with genital warts. HPV 6 and 11 are more commonly associated with genital warts and are also responsible for approximately 90% of these lesions. Despite a series of modalities available to treat HPV, that range from topical to immunotherapeutic modalities to surgically destructive procedures, there is no promising, stand-alone modality which still is a cause of dilemma for Dermatologists while treating warts. The present article reviews all the treatment modalities commonly applied in practice and also the areas less explored by their level of evidences.

Keywords: Anogenital, Human papillomavirus, Immunotheraputic modalities, Verruca

INTRODUCTION

The HPV causes benign, warty, epithelial growth at mucosal and cutaneous surfaces. There is a myriad of treatment options which employs individual and combination modalities to curb new break-outs and to get rid of existing warty growth [1]. In the present narrative review, treatment therapies are tabulated in [Table/Fig-1] based on their route of action, namely 'Topical', 'Intralesional' 'Systemic' and 'Destructive'. The level of evidence which also indicates the extent of utilisation and outcome has been deduced. Level of evidence has been cited following the 'hierarchy of evidence' pyramid [2] (where, level I is the apex of the pyramid indicating modality has been researched through meta-analysis and systematic reviews, level II shows that, randomised controlled, double-blind studies have been performed, level III implies evidence of cohort studies, level IV case control, level V case series, case reports and so on are levels below it [2].

Topical	Intralesional	Systemic	Destructive
Podophyllotoxin/ podophyllin	BCG vaccine, PPD	Zinc	Cryotherapy
Imiquimod	MMR vaccine	Echinacea	Radiofrequency Ablation (RFA)
Sinecathechins	Vitamin D3	HPV vaccines	Laser (CO_2, PDL, Nd:Yag)
Thuja extract (white cedar tree)	Candida antigen extract	Propolis	Nano pulse stimulation
Retinoic acid		Levamisole	
5-FU		H2 receptor blockers (cimetidine, ranitidine)	

[Table/Fig-1]: Various modalities in treatment of warts.
BCG: Bacillus Calmette-Guerin; PPD: Purified protein derivative; MMR: Measles, Mumps, Rubella; PDL: Pulsed dye laser; Nd:Yag: Neodymium-doped yttrium aluminium garnet; FU: Fluorouracil

A study done by Thappa DM and Chiramel MJ, to establish the effectiveness of a single modality-like role of immunotherapy and other such therapies that utilises comparison of topical, intralesional and entities like lasers [1]. So far, none of them have proven to be ineffective, yet none of them promises eradication without recurrence. Yet still, some of them are extensively utilised compared to others because of definite advantage over others that include safety, easy accessibility, ease of procurement and lower degree of skills required to deliver treatment.

TREATMENT MODALITIES

Topical

Podophyllotoxin/podophyllin (level II): According to a Randomised Controlled Trial (RCT) that compared efficacy and cost-effectiveness of podophyllotoxin 0.5% solution: a home based treatment (self-applied by patient) and podophyllotoxin 0.15% cream, that was applied in clinic set-up (by clinician), self-treatment of anogenital warts with podophyllotoxin demonstrated greater efficacy and cost-effectiveness than clinic-based treatment with podophyllin, but local side effects were seen in 24% of subjects [3]. In another RCT, podofilox (podophyllotoxin 0.5% cream, self-applied by patients) outperformed placebo in clearing condylomata acuminata, clearing 74% of the condylomata compared to only 18% of the condylomata in the placebo group. Podofilox was found to be more effective and economical than clinic treatments for condylomata acuminata when compared to self administered podophyllotoxin and 25% podophyllin applied [4].

Imiquimod (level I, II): In a multicentric, double-blind, randomised controlled study, using 5% imiquimod cream three times per week for 16 weeks was shown to be more successful than applying 1% imiquimod cream for the treatment of genital warts [5,6]. Similar to this, Moore RA et al., came to the conclusion that, imiquimod is a successful home-based treatment option for genital warts after conducting a systematic study [7]. Upto 76% of the patients had completely resolved warts. Although, it is safe and effective to use in children and during pregnancy [8,9], there have been reports of adverse effects including burning, discomfort, erythema, and depigmentation that resembles vitiligo [1].

Sinecatechins (level II, III): In a clinical trial, 15% sinecatechin ointment (veregen) demonstrated good therapeutic efficacy and safety for the treatment of genital and perianal warts with clearance rates of >50% by eradicating baseline warts, as well as, combating newly developed warts, with a recurrence rate that appeared to be lower [7] than that of imiquimod and podophyllotoxin [10]. Similarly, in another, randomised, double-blind, phase 3 clinical studies, 53.6% of patients, who received sinecatechins 15% ointment for external genital and perianal warts had total removal of both pre-existing and newly appearing

warts, and 93.2% of these patients had complete clearance of external genital warts and had maintained clearance at 12 weeks after therapy [11]. Negative effects of sinecatechins ointment were mild to moderately severe local skin responses. Sinecatechins ointment's mode of action is uncertain, necessitating more clinical and research trials [11].

Thuja (white cedar tree) extract (level V): The use of thuja occidentalis extract (white cedar tree), a flavinoid, as a phytosomal preparation has been tested In both an open study and a double-blind clinical study, the effects of thuja occidentalis on verruca pedis were examined [12,13]. The results of the clinical study revealed that, the ethanolic crude extract of thuja occidentalis was successful in reducing verruca size and clearing. Human keratinocyte cell growth induced the toxic effects of thuja occidentalis, which were concentration dependant [13].The biological tests and clinical research findings reveal a strong association between safety and effectiveness in the treatment of verruca pedis [12-14]. These promising findings require more research with more patients over a longer period of time

Retinoic acid (level I,V): Retinoids have historically been widely used to treat other forms of warts their utility in genital warts is examined in a systematic meta-analysis review of three randomised controlled trials and three prospective cohort studies [15]. Out of the six publications, that were analysed indicated full response rates of 100% for systemic etretinate and 56% for isotretinoin. Etretinate used topically did not cause complete remission. Further research is needed to ascertain their precise function and the most efficient regimen for each derivative [15]. An open, randomised trial comparing the effectiveness and safety of oral isotretinoin with topical isotretinoin for the treatment of plane warts in 40 individuals with numerous plane warts, oral isotretinoin shows a better and quicker response [16]. In an open study, 10 patients with 118 plantar warts were treated with topical adapalene (0.1% gel) under occlusion. The results of the treatment were assessed every week until all warts had disappeared, and it was discovered that, this took 39±15 days in total. Adapalene did not have any negative side effects such as infection, erythema, or the creation of scars [17].

5-Fluorouracil (FU) (level I, II): The effectiveness and safety of 5-FU topical treatment were assessed in a Cochrane review for genital warts in non immunocompromised patients [18]. The main findings of six trials involving 988 patients (645 women and 343 men) and reporting eight comparisons were found that, topical use of 5-FU has a therapeutic effect, but further research is required to precisely define the advantages and hazards [18]. In a study, to test the effectiveness of microneedling alone, its combination with 5-fluorouracil solution, and 5-fluorouracil intralesional injection in the treatment of plantar warts, complete response in 86.7% of group C (microneedling+ intralesional 5-FU) compared to 76.7% and 70% in group A (IL 5-FU) and B (microneedling), respectively was seen. No recurrence was noted across all groups, indicating that microneedling may be employed as an adjunctive or alternative therapeutic approach for the treatment of plantar warts [19]. In a study that compared topical 5% 5-Fluorouracil with needling versus 30% Trichloroacetic Acid (TCA) with needling in plantar warts, the results showed that, both, topical 5% 5-FU and 30% TCA are highly effective, when used in conjunction with needling to remove plantar warts. However, 30% TCA offers the benefit of beginning treatment right away and clearing plantar warts completely with fewer side effects [20]. In a two step procedure: 1) Systematic literature analysis; and 2) Meta-analysis of the Randomised Controlled Studies (RCTs) evaluation of the effectiveness and benefits of combination containing 0.5% 5-FU and 10% Salicylic Acid (SA) in the therapy of common and plantar warts, the results revealed that, the therapeutic effect in common warts was 63.4% response (complete healing), compared to 23.1% for the 5-FU-free controls, respectively. In RCTs, the response for plantar warts was 63.0% vs 11.0% [21]. The combination of 5-FU and SA is an efficient and advantageous therapy for both, common and plantar warts, with a similar outcome also being discovered for plantar warts [21].

Intralesional

BCG Purified Protein Derivative (PPD) (level IV, V): There was a 39.7% resolution with BCG vs. a 13.7% resolution with placebo in a single-blind, placebo-controlled trial by Sharquie KE et al., comprising 154 individuals with cutaneous warts (common, plantar, and plane warts) [22]. Another placebo-controlled experiment (N=80) using topically applied BCG paste (monthly for six weeks) demonstrated 65% and 45% clearance of common warts and plane warts, respectively, without any side-effects [23] However, Daulatabad D et al., analysed on seven Indian patients revealed a significant prevalence of flu-like symptoms, raising concerns about the medication's safety in tuberculosis-endemic nations like India [24]. At the end of four injections at a dose of 2.5 units into a few warts every two weeks, PPD or tuberculin intralesional injection into difficult to treat cutaneous warts (palmoplantar warts, periungual warts, facial warts (>10 lesions), verucca vulgaris (>10 lesions), and verruca plana (>10 lesions) resulted in 76% complete resolution and a 6 month follow-up revealed only one recurrence [1].

MMR vaccine (level V): By injecting 0.5 mL of MMR vaccine into each cutaneous wart once every two weeks for up to five sittings, Nofal A et al., were able to achieve a 63% full remission [25]. Within three sessions, Gamil H et al., found complete removal in 87% of the 40 patients with numerous plantar warts [26]. In a research by Shaheen MA et al., which compared the MMR vaccination with intralesional pure protein derivative and saline in 10 patients each [27], the remission rate when MMR was injected in the lesions and at a distal (non lesional) site was 60% with PPD and 80% and 40% with MMR, respectively, and 0% with saline [1]. Clinical research on the effectiveness, cost-effectiveness, and promising safety profile of the measles, mumps, and rubella vaccine in the treatment of common warts came to encouraging conclusions [28]. The adverse effects described included pain, itching, erythema, and symptoms similar to the flu [1].

Vitamin D3 (level IV, V): A total of 64 individuals with resistant warts of various sizes participated in a research in which the base of the wart was injected with 0.2 to 0.5 mL of a vitamin D3 solution (600,000 IU, 15 mg/mL). The typical amount of shots needed to get a full resolution was 3.66. In all cases, remote warts completely disappeared [29]. Similar to this, Fathy G et al., determined that, intralesional vitamin D3 injection in multiple recalcitrant plantar warts produced superior results to intralesional injection of candida antigen in 60 randomly chosen patients with multiple recalcitrant plantar warts, coming to the conclusion that, such an injection is beneficial [30]. To clarify the precise mechanism of action of vitamin D3 and determine the appropriate dose, frequency, and number of sessions required to obtain the best response, more thorough case-control studies, as well as, in-vivo and in-vitro investigations, are essential.

Candida antigen extract (level V): At initial visit, 0.3 mL of candida antigen extract is intralesionally injected to cause a cellular response and clearance of warts, after that 0.3 mL of candida extract is injected into the most prominent wart every three weeks. In a phase 1 study on cutaneous warts, 82% of patients had clearance of lesions present distally, according to Kim KH et al., [31]. Muñoz Garza FZ et al., observed 71% full resolution after injecting candida antigen intralesionally in 220 youngsters, with an average of 2.7 sittings [32]. A distant response due to the intralesional candida was seen in 21% and half of them had full recovery, pain and discomfort during the injection were the most frequent adverse effects. However, severe side effects like painful purple digits and depigmentation that resembles vitiligo have also been documented. Post-immunotherapy revealed cicatrix is another infrequent adverse event mentioned by Signore RJ (PIRC) [33]. When immunotherapy begins to work and

the wart begins to heal, the scar left behind by earlier damaging operations on the wart becomes obvious. It is incorrect to mistakenly ascribe the scar to the immunotherapy itself [1].

Systemic

Zinc (level II, IV): Warts on the skin and in the genitalia can be treated with oral and topically applied zinc. It has been demonstrated that, people with recurring warts were zinc deficient. In two randomised placebo-controlled studies [34,35], oral zinc sulphate at a dosage of 10 mg/kg/day was given. Approximately, 84%-87% of patients experienced full wart resolution in two months. In addition to being used alone, it has also been used with other modalities including imiquimod, podophyllin, and cryotherapy. It performs better than cimetidine [36]. Three times per day for four weeks, cutaneous warts were treated with a topical 5% and 10% zinc solution with only a 5% and 11% response, respectively. Salicylic acid-lactic acid and topical zinc oxide 20% ointment both had nearly comparable effectiveness [1].

Echinacea (level II): Echinacea (purple coneflower) has three commercially used forms: Echinacea Purpurea (EP), Echinacea Angustifolia (EA), and echinacea pallida [37,38]. Echinacea is used mostly for prevention or treatment of the common cold and acute upper respiratory infection [38,39]. Echinacea appears to be a relatively safe herbal medicine, In a prospective randomised trial by De Rosa N et al., on all patients diagnosed with a genital condylomatosis were enrolled and the echinacea purpurea immunomodulatory effect was widely demonstrated [40]. In-vitro studies have shown that, EP acts directly on several cell types, including natural killer cells, polymorphonuclear leukocytes, and macrophages [41,42]. EP induces proliferation of T cells. This has been conferred to the activation of macrophages that stimulates production of Interferon gamma (IFN-γ) and, consequently, secondary activation of T lymphocytes. IFN-γ is one of the fundamental mediators for latency prevention consequently, reducing the relapse risk of Herpes Simplex Virus (HSV) lesions. In conclusion, echinacea promotes a protective immune response to allow rapid viral clearance from genital areas surrounding lesions and treatment zones. In individuals being treated for genital condylomatosis, dried root extracts of EP and EA appear to be an effective adjuvant therapy in lowering relapse of lesions [40].

HPV Vaccine (level III): Use of the quadrivalent HPV vaccination, which contains the L1 proteins of HPV types 6, 11, 16, and 18, has been widespread in nations like Denmark, where the frequency of genital warts has decreased [43]. With each HPV vaccination dosage, the likelihood of developing warts dropped. Both, immunocompetent and immunocompromised people who received the HPV vaccination and had cutaneous warts have had their warts disappear. With the introduction of nonavalent HPV vaccines against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, it is anticipated that HPV-related illnesses, such as warts, would continue to reduce [1]. 12-18 year-old women were enrolled in a cohort trial in Belgium from 2007 through December 2008 to show the preventive usage and ongoing effectiveness of the quadrivalent HPV vaccination (qHPV) on genital warts. Incidence rates of Gulf War Syndrome (GWs) dramatically dropped overall during the pre and post vaccination eras [44].

Propolis (level II): Propolis is a resinous material collected by bees from plant buds [45]. It is applied externally and is widely known for its antiviral, antibacterial, anti-inflammatory and antifungal properties [46]. Zedan H et al., evaluated the effectiveness of propolis and echinacea in treating various kinds of warts with oral propolis, echinacea, or placebo in a single-blind, randomised, study including 135 patients [47]. Propolis treatment cured 75% and 73%, respectively, of the patients with plantar and common warts. These results showed that, propolis is an efficient and secure immunomodulating therapy for plantar and common warts, and they were much better than those obtained with echinacea treatment or a placebo.

Levimasole (level IV, V): Levamisole was initially developed as an antihelminthic drug, but it was quickly shown to have immunomodulatory properties, which made it useful for treating a variety of dermatological conditions. Levamisole had a response rate of about 60% in cutaneous warts when given at a dosage of 2.5-5 mg/kg/day for three consecutive days every two weeks for 4-5 months. However, there was no difference between levamisole 150 mg/day for three days every alternate week and a placebo in a double-blind research by Schou M and Helin P [48]. Over 12 cycles of levamisole, 5 mg/kg body weight on three consecutive days every two weeks, was administered to 22 individuals with multiple verruca vulgaris. It was highlighted that, conflicting reports in the literature about the usage of levamisole in verruca patients [49] may be caused by various patient selection criteria and varying lengths of therapy [50]. Levamisole can result in a flu-like illness, alopecia, arthralgia, nausea, stomach cramps, rash, and taste changes [1].

H2 receptor blockers (level I): Warts have been treated with H2 blockers such as cimetidine and ranitidine in doses of 20-40 mg/kg/day for 3-4 months, with success rates ranging from 30%-87% [51,52]. Ranitidine has only been the subject of exploratory research with dubious results. However, inconsistent reports of little to no response, particularly to low dose cimetidine, are seen in other double-blind investigations [53,54]. There are reports of safety and somewhat greater effectiveness in youngsters than in adults. A 2007 systematic review [55] found inadequate support for the effectiveness of cimetidine and ranitidine in the treatment of viral warts. Mild side effects included headache, nausea, and vomiting [1].

Destructive

Cryotherapy (level II, III): In 200 patients randomised into two groups of 100 each who were undergoing cryotherapy for viral warts, the traditional freeze method and a 10 seconds sustained freeze were compared. The results showed that, the 10 second sustained freeze was more effective than the traditional freeze method, but it was also more painful [56].

Radiofrequency (level II): Arora AK et al., in 'cryotherapy versus RFA: which is more effective for treating plantar warts', after randomly splitting 50 plantar wart patients into two groups of 25, the results revealed that, RFA was superior than cryotherapy for treating plantar warts and yielded quicker subjective and objective outcomes [57]. Jaiswal P et al., in randomised control trial of 75 cases of plane warts with age >12 years, divided into three groups, compared the efficacy and adverse effect of RFA, electrodesiccation, and cryosurgery in the treatment of cutaneous warts. Complete cure in group A (RFA) was 22 (95%), in group B (electrodesiccation) was 17 (73%), and in group C (cryosurgery) was 14 (58%) concluded radiofrequency to have the highest cure rate [58].

Laser (level II, V): In a review paper by Iranmanesh B et al., various laser therapy methods, including 22 pulsed dye lasers, 10 Nd:YAG lasers, three Er:YAG lasers, 14 CO_2 lasers, and one systematic review, were assessed [59]. According to the kind of laser employed, complete response rates ranged from 0% to 100%, 9.1% to 100%, 83.3% to 100%, and 59.15% to 100% for PDL, Nd:YAG, Er:YAG, and CO_2 lasers, respectively. Regarding effectiveness and recurrence rate, there was no discernible difference between laser therapy and other treatment approaches. Combining laser treatment with immunomodulators, keratolytic drugs, and photodynamic therapy might be beneficial, particularly in immunocompromised individuals with resistant and recurring lesions. PDL experiences the fewest negative consequences in comparison to other types of lasers [59]. To determine the effectiveness and safety of PDL treatment for viral warts, 120 wart patients who received pulsed dye laser treatment participated in a prospective, non blinded, non randomised trial. Overall, compared to adult warts, simple warts, and non old warts, paediatric warts, recalcitrant warts, and old warts had better response rates [60]. A

total of 46 individuals with numerous plantar warts participated in a comparison research using the pulsed dye laser and the Nd:YAG laser for the treatment of resistant plantar warts. Lesions from each patient were split into two groups, one of which received Nd:YAG treatment and the other PDL. A maximum of six laser treatments were performed every two weeks. The findings revealed that, current treatment approaches are frequently intrusive, ineffective in treating plantar warts, and need lengthy recuperation time. Plantar warts that are resistant to treatment respond well to PDL and Nd:YAG laser therapy. Nd:YAG is more unpleasant and exhibits more problems, whereas, PDL is safer and less uncomfortable but requires more sessions [61].

Nano-Pulse Stimulation (NPS) therapy (pilot study): Nanosecond pulsed electric fields are used to cells and tissues during NPS therapy to cure cellular lesions in the epidermis and dermis without damaging non cellular substances like collagen and fibrin. A research looked at data from clinical trials detailing how NPS treatment affected both healthy skin and three distinct skin lesions. In 60 days, 60% of the warts treated with NPS inpilot experiments disappeared entirely, majority of warts were resistant to removal with one or more liquid nitrogen treatment but, by 60 days of following treatment, the majority of these 23 resistant warts that had NPS therapy was completely disappeared. NPS treatment has shown promise in pilot study curing warts on the hands and feet, and a pivotal trial with many more subjects is underway [62], the outcome of the various treatment modalities is given in [Table/Fig-2].

Modality	Site	Result	Level of evidence
Topical			
Podophyllotoxin/ podophyllin	Anogenital warts	Effective	Level II
Imiquimod	Anogenital warts, cutaneous warts	Effective with S/E	Level I, II
Sinecatechins	Anogenital warts, cutaneous warts	S/E > efficacy	Level II, III
Thuja extract	Verruca pedis	Further studies needed to reinforce efficacy	Level V
Retinoids	Anogenital warts, cutaneous warts	Effective with S/E	Level I, V
5-FU	Anogenital warts, cutaneous warts	Effective with combination modalities	Level I, II
Intralesional			
BCG vaccine/ PPD	Anogenital warts, cutaneous warts	Safety concerns >efficacy	Level IV, V
MMR vaccine	Cutaneous warts	S/E >efficacy	Level V
Vitamin D3	Recalcitrant cutaneous warts	Effective (further studies needed)	Level IV, V
Candida antigen extract	Cutaneous warts	ADR >Efficacy	Level V
Systemic			
Oral zinc	Anogenital warts, cutaneous warts	Equivocal (effective with combination modalities)	Level II, IV
Echinacea	Anogenital warts, cutaneous warts	Effective as an adjuvant modality	Level II
HPV vaccine	Anogenital warts	Effective	Level III
Propolis	Cutaneous warts	Effective with combination modalities (further studies needed	Level II
Levimasole	Cutaneous warts	Equivocal	Level IV, V
H2 receptor blocker (cimetidine, ranitidine)	Cutaneous warts	Inconclusive	Level I
Destructive			
Cryotherapy	Cutaneous warts	Effective with combination modalities	Level II, III
Radiofrequency Ablation (RFA)	Cutaneous warts	Effective with combination modalities	Level II
Lasers	Cutaneous warts	Effective with combination modalities	Level I, V
Nano-Pulse Stimulation (NPS) therapy	Recalcitrant cutaneous warts	Further studies needed to reinforce efficacy	Pilot study [57]

[Table/Fig-2]: Treatment modalities with level of evidence.
ADR: Adverse drug reaction; S/E: Side effect

CONCLUSION(S)

All these studies/ articles suggest that, after laying out the various treatment options, it can be inferred that no therapeutic option can be so far identified as ineffective, combination modalities rather than single therapeutic options for treating genital and cutaneous warts offer a long term resolution, although, recurrence free options are yet not warranted. Also, apart from conventional, new therapies are arriving but the evidence is not sufficient. In addition, there is an advent of herbal and homeopathic treatment options like propolis, echinacea, thuja extract and pilot study in area of NPS for treating warts have been carried out hence there is a need for well-planned double blind studies in these areas.

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